Complete Summary

GUIDELINE TITLE

Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians.

BIBLIOGRAPHIC SOURCE(S)

Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK, Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2008 Nov 18;149(10):725-33. [100 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s)/intervention(s) for which important revised regulatory and/or warning information has been released.

- June 17, 2008 – Antipsychotics (conventional and atypical]): The U.S. Food and Drug Administration (FDA) notified healthcare professionals that both conventional and atypical antipsychotics are associated with an increased risk of mortality in elderly patients treated for dementia-related psychosis. The prescribing information for all antipsychotic drugs will now include information about the increased risk of death in the BOXED WARNING and WARNING sections.

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QUALIFYING STATEMENTS
IMPLEMENTATION OF THE GUIDELINE
INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

SCOPE

DISEASE/CONDITION(S)

Depressive disorders including:

- Acute, continuation, and maintenance phases of major depressive disorder (MDD)
- Dysthymia
- Subsyndromal depression
- Accompanying symptoms such as anxiety, insomnia, or neurovegetative symptoms

GUIDELINE CATEGORY

Management
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Pharmacology
Psychiatry

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To synthesize the evidence for the following key questions:

Key Question 1: For adults with major depressive disorder (MDD) or dysthymia, do commonly used medications for depression differ in efficacy or effectiveness in treating depressive symptoms?

Key Question 2a: For adults with a depressive syndrome, do antidepressants differ in their efficacy or effectiveness for maintaining response or remission (preventing relapse or recurrence)?

Key Question 2b: For adults receiving antidepressant treatment for a depressive syndrome that has not responded (acute phase), has relapsed (continuation

phase), or has recurred (maintenance phase), do alternative antidepressants differ in their efficacy or effectiveness?

Key Question 3: Do second-generation medications used to treat depression differ in their efficacy or effectiveness for treating accompanying symptoms, such as anxiety, insomnia, and neurovegetative symptoms?

Key Question 4: How do the efficacy, effectiveness, or harms of treatment with antidepressants for a depressive syndrome differ for the following subpopulations: elderly or very elderly patients; other demographic groups, defined by age, race or ethnicity, or sex; and patients with medical comorbid conditions, such as ischemic heart disease or cancer?

Key Question 5: For adults with a depressive syndrome, do commonly used antidepressants differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to nausea; diarrhea; headache; tremor; daytime sedation; decreased libido; failure to achieve orgasm; nervousness; insomnia; and more severe events, including suicide.

TARGET POPULATION

Patients with depressive disorders

INTERVENTIONS AND PRACTICES CONSIDERED

1. Selection of second-generation antidepressants
2. Regular monitoring of therapeutic response and adverse effects beginning within 1 to 2 weeks of initiation of therapy
3. Treatment modification if inadequate response
4. Continued treatment according to risk for relapse or recurrence

MAJOR OUTCOMES CONSIDERED

- Efficacy and effectiveness of antidepressants
- Quality of life
- Speed of response for acute phase
- Maintenance of response or remission
- Risk for harms and adverse effects

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): These recommendations are based on the systematic evidence review by Gartlehner and colleagues and the Agency for Healthcare Research and Quality–sponsored RTI International–University of North Carolina Evidence-based Practice Center (EPC) evidence report (see the "Availability of Companion Documents" field).

Data Sources

EPC staff searched MEDLINE, EMBASE, PsychLit, Cochrane Central Register of Controlled Trials, and International Pharmaceutical Abstracts from 1980 to April 2007. Medical Subject Heading terms were used when available and keywords when appropriate. Terms for depressive disorders were combined with a list of 12 specific second-generation antidepressants—bupropion, citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine—and their specific trade names. Electronic searches were limited to "adult 19+ years," "human," and "English language."

EPC staff manually searched reference lists of pertinent review articles and letters to the editor and used the Center for Drug Evaluation and Research database (up to April 2007) to identify unpublished research submitted to the U.S. Food and Drug Administration. The Scientific Resource Center invited pharmaceutical manufacturers to submit dossiers on completed research for each drug. The authors received dossiers from 3 pharmaceutical companies (Eli Lilly and Company, Indianapolis, Indiana; GlaxoSmith-Kline, Philadelphia, Pennsylvania; and Wyeth, Madison, New Jersey).

Study Selection

Two persons independently reviewed abstracts and relevant full-text articles. To assess efficacy or effectiveness regarding response, speed of onset, remission, maintenance of remission, and quality of life, head-to-head controlled trials of at least 6 weeks' duration that compared 1 drug with another were included. Because head-to-head evidence was lacking for many comparisons, placebo-controlled trials for indirect comparison models were included. To assess harms (specific adverse events, rates of adverse events, and discontinuations attributable to adverse events), the authors also examined data from observational studies with at least 100 participants and follow-up of at least 12 weeks. To assess differences of benefits and harms in subgroups and patients with accompanying symptoms, both head-to-head and placebo-controlled trials were reviewed. Meta-analyses were included if found to be relevant for a key question and of good or fair methodological quality.

If both reviewers agreed that a study did not meet eligibility criteria, it was excluded. Also excluded were studies that met eligibility criteria but were reported only as an abstract. Investigators resolved disagreements about inclusion or exclusion by consensus or by involving a third reviewer.

NUMBER OF SOURCE DOCUMENTS

This guideline is based on evidence derived from 203 studies.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

This guideline rates the evidence and recommendations by using a slightly modified version of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (see "Rating Scheme for the Strength of the Recommendations" field, below).

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Data Extraction and Quality Assessment

The authors used a structured, Web-based data abstraction form (SRS 4.0, TrialStat, Ottawa, Ontario, Canada) onto which trained reviewers abstracted data from each study and assigned an initial quality rating. A senior reviewer read each abstracted article, evaluated completeness of data abstraction, and confirmed the quality rating. Investigators resolved disagreements by discussion and consensus or by consulting an independent party.

The internal validity (quality) of trials was assessed on the basis of predefined criteria and applied ratings of good, fair, or poor. Primary elements of quality assessment included randomization and allocation concealment, similarity of compared groups at baseline, blinding, use of intention-to-treat analysis, and overall and differential loss to follow-up. To assess observational studies, the authors used criteria involving selection of case patients or cohorts and control participants, adjustment for confounders, methods of outcomes assessment, length of follow-up, and statistical analysis. Studies with a fatal flaw in 1 or more categories were rated as poor quality (Appendix Table 1 in the original guideline document, available at www.annals.org) and were not included in the analyses for this review unless no other head-to-head evidence was available. To identify effectiveness studies, a tool that distinguishes efficacy trials from effectiveness studies on the basis of certain elements of study design was used. Such studies have greater generalizability of results than efficacy trials because they enroll less selected study populations, use treatment modalities that mimic clinical practice, and assess health outcomes along with adverse events.

Lacking clear definitions about the equivalence of dosages among second-generation antidepressants in the published literature, reviewers developed a roster of low, medium, and high dosages for each drug based on the interquartile dosing range. This roster, which does not indicate dosing equivalence, was used

to detect gross inequalities in dosing that could affect comparative efficacy and effectiveness.

Data Synthesis

If data were sufficient, meta-analyses of head-to-head comparisons were conducted. Efficacy outcomes included the relative benefit of achieving response (more than 50% improvement from baseline), which reflects the ratio of benefits in one treatment group to benefits in another, and the weighted mean difference of changes on the Hamilton Depression Rating Scale or the Montgomery-Asberg Depression Rating Scale.

For each meta-analysis, the authors conducted a test of heterogeneity (I^2 index) and applied both random- and fixed-effects models. The random-effects results were reported because the results from both models were very similar in all meta-analyses. Publication bias was assessed by using funnel plots and the Begg adjusted rank correlation test based on the Kendall coefficient.

Because no head-to-head evidence was available for the majority of drug comparisons, adjusted indirect comparisons were conducted. Meta-regressions of placebo-controlled trials were employed by using individual drugs as covariates. When the number of trials was insufficient for meta-regressions, modified network meta-analysis was used. Evidence suggests that indirect comparisons agree with head-to-head trials if component studies are similar and treatment effects are expected to be consistent in patients included in different trials, although these assumptions are usually not verifiable.

All statistical analyses used StatsDirect Statistical Software program, version 2.3.8 (StatsDirect, Sale, United Kingdom); Stata, version 9.1 (StataCorp, College Station, Texas); and SAS, version 9.1 (SAS Institute, Cary, North Carolina).

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Guideline developers systematically reviewed the literature to address the questions stated above.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

American College of Physicians' Clinical Practice Guidelines Grading System*		
Quality of Evidence	**Strength of Recommendation**	
	Benefits	**Benefits**

American College of Physicians' Clinical Practice Guidelines Grading System*		
Quality of Evidence	**Strength of Recommendation**	
	Clearly Outweigh Risks and Burden OR Risks and Burden Clearly Outweigh Benefits	**Finely Balanced with Risks and Burden**
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I recommendation	

*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was approved by the American College of Physicians Board of Regents on July 13, 2008.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The strength of the evidence (**high, moderate, low, insufficient evidence to determine benefits or risks**) and strength of recommendations (**strong, weak,**

I-recommendation) are defined at the end of the "Major Recommendations" field.

Recommendation 1: *The American College of Physicians recommends that when clinicians choose pharmacologic therapy to treat patients with acute major depression, they select second-generation antidepressants on the basis of adverse effect profiles, cost, and patient preferences* **(Grade: strong recommendation; moderate-quality evidence)**.

Various approaches, including pharmacotherapy, psychotherapy, and cognitive behavioral therapy, are effective for treatment of depression. Existing evidence does not justify the choice of any second-generation antidepressant over another on the basis of greater efficacy and effectiveness. Efficacy and effectiveness of these agents do not differ among subgroups based on age, sex, or race or ethnicity. However, differences have been reported among some medications in mild (constipation, diarrhea, dizziness, headache, insomnia, nausea, and somnolence) to major (sexual dysfunction and suicidality) adverse effects. Bupropion is associated with a lower rate of sexual adverse events than fluoxetine or sertraline, whereas paroxetine has higher rates of sexual dysfunction than fluoxetine, fluvoxamine, nefazodone, or sertraline. In addition, selective serotonin reuptake inhibitors (SSRIs) are associated with an increased risk for suicide attempts compared with placebo. Physicians and patients should discuss adverse event profiles before selecting a medication.

Recommendation 2: *The American College of Physicians recommends that clinicians assess patient status, therapeutic response, and adverse effects of antidepressant therapy on a regular basis beginning within 1 to 2 weeks of initiation of therapy* **(Grade: strong recommendation; moderate-quality evidence)**.

The U.S. Food and Drug Administration advises that all patients receiving antidepressants be closely monitored on a regular basis for increases in suicidal thoughts and behaviors. Such monitoring should begin 1 to 2 weeks after initiation of therapy. Patients should be monitored for the emergence of agitation, irritability, or unusual changes in behavior, because these symptoms can indicate that the depression is getting worse. The risk for suicide attempts is greater during the first 1 to 2 months of treatment.

Recommendation 3: *The American College of Physicians recommends that clinicians modify treatment if the patient does not have an adequate response to pharmacotherapy within 6 to 8 weeks of the initiation of therapy for major depressive disorder* **(Grade: strong recommendation; moderate quality evidence)**.

One of the most important aspects of care is assessing the response to treatment and making necessary changes in therapy if the response is not sufficient after adequate treatment. Clinicians should consider whether addition of other therapeutic modalities may be indicated. The response rate to drug therapy may be as low as 50%. In addition, the evidence is insufficient to determine which patient factors can reliably predict response or nonresponse to an individual drug. Multiple pharmacologic therapies might be required for patients who do not respond to first- or second-line treatments. Insufficient evidence exists to prefer

one agent over another as second-line therapy. Table 2 in the original guideline document summarizes the durations and dosages of treatments used in the trials reviewing the treatment of major depressive disorders (MDD).

Recommendation 4: *The American College of Physicians recommends that clinicians continue treatment for 4 to 9 months after a satisfactory response in patients with a first episode of major depressive disorder. For patients who have had 2 or more episodes of depression, an even longer duration of therapy may be beneficial* **(Grade: strong recommendation; moderate-quality evidence)**.

Duration of therapy depends on the risk for relapse or recurrence. Patients who achieve remission with acute-phase treatment should continue receiving antidepressant therapy for 4 to 9 months to prevent relapse. No evidence indicates differences among second-generation antidepressants in preventing relapse (loss of response during continuation-phase treatment) or recurrence (loss of response during maintenance-phase treatment). Patients who have had 2 or more episodes may benefit from a longer duration of therapy (years to lifelong). Table 3 in the original guideline document summarizes the durations and dosages of treatments used in the trials that reviewed the comparative efficacy and effectiveness of second-generation antidepressants for treating recurrent and treatment-resistant depression.

Definitions:

American College of Physicians' Clinical Practice Guidelines Grading System*		
Quality of Evidence	**Strength of Recommendation**	
	Benefits Clearly Outweigh Risks and Burden OR Risks and Burden Clearly Outweigh Benefits	**Benefits Finely Balanced with Risks and Burden**
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks	I recommendation	

*Adopted from the classification developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) workgroup.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate pharmacologic treatment of the acute, continuation, and maintenance phases of depressive disorders using second-generation antidepressants

POTENTIAL HARMS

Adverse Effects of Medications

Adverse Events

- The most commonly reported adverse events included constipation, diarrhea, dizziness, headache, insomnia, nausea, sexual adverse events, and somnolence. Nausea and vomiting were the most common reasons for discontinuation in efficacy studies.
- Most of the second-generation antidepressants had similar adverse events, with some differences in the incidence of specific adverse events:
    - *Venlafaxine* had a higher incidence of nausea and vomiting than other selective serotonin reuptake inhibitors (SSRIs).
    - *Sertraline* had a higher rate of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, or venlafaxine.
    - *Mirtazapine* and *paroxetine* resulted in higher weight gain than sertraline, trazodone, or venlafaxine.
    - *Trazodone* was associated with a higher incidence of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, or venlafaxine.

Severe Adverse Events

- *Paroxetine* was associated with an increased risk for sexual dysfunction.
- SSRIs are associated with an increased risk for suicide attempts.
- Seizures, cardiovascular risks (increases in systolic or diastolic blood pressure and pulse or heart rate), hyponatremia, hepatotoxicity, or the serotonin

syndrome are scarce but should be kept in mind when patients are being treated with a second-generation antidepressant.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment.
- The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Patient Resources
Personal Digital Assistant (PDA) Downloads
Staff Training/Competency Material

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK, Clinical Efficacy Assessment Subcommittee of American College of Physicians. Using second-

generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2008 Nov 18;149(10):725-33. [100 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 Nov 18

GUIDELINE DEVELOPER(S)

American College of Physicians - Medical Specialty Society

SOURCE(S) OF FUNDING

American College of Physicians

GUIDELINE COMMITTEE

Clinical Efficacy Assessment Subcommittee of the American College of Physicians

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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Subcommittee Members: Douglas K. Owens, MD, MS (*Chair*); Donald E. Casey Jr., MD, MPH, MBA; Paul Dallas, MD; Thomas D. Denberg, MD, PhD; Mary Ann Forciea, MD; Robert H. Hopkins Jr., MD; William Rodriguez-Cintron, MD; and Paul Shekelle, MD, PhD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Grants received: V. Snow (Atlantic Philanthropies, Novo Nordisk, Boehringer Ingelheim, Centers for Disease Control and Prevention, Sanofi Pasteur, Endo). Any conflict of interest of the group members was declared, discussed, and resolved.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Annals of Internal Medicine Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Gerald Gartlehner, MD, MPH; Bradley N. Gaynes, MD, MPH; Richard A. Hansen, PhD, RPh; Patricia Thieda, MA; Angela DeVeaugh-Geiss, MS; Erin E. Krebs, MD, MPH; Charity G. Moore, PhD, MSPH; Laura Morgan, MA; and Kathleen N. Lohr, PhD. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. Ann Intern Med. 2008 November 18;149(10):734-750. Electronic copies: Available from the Annals of Internal Medicine Web site.
- Gerald Gartlehner, MD, MPH; Richard A. Hansen, PhD; Patricia Thieda, MA; Angela M. DeVeaugh-Geiss, MS; Bradley N Gaynes, MD, MPH; Erin E. Krebs, MD; Linda J. Lux, MPA; Laura C. Morgan, MA, MPH; Janelle A. Shumate, MD, MPH; Loraine G. Monroe; Kathleen N. Lohr, PhD. Comparative effectiveness of second-generation antidepressants in the pharmacologic treatment of adult depression. (Prepared by the RTI International-University of North Carolina Evidence-based Practice Center under contract 290-02-0016.) Rockville, MD: Agency for Healthcare Research and Quality; January 2007. AHRQ publication no. 07-EHC007-EF. Electronic copies: Available from the AHRQ Web site.

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

A collection of Recommendation Summaries for all current American College of Physicians clinical guidelines is available for Personal Digital Assistant (PDA) download from the American College of Physicians Web site.

PATIENT RESOURCES

The following is available:

- Summaries for patients. Use of drugs to treat depression: guidelines from the American College of Physicians. Ann Intern Med 2008 November 18; 149(10):I-56. Available from the Annals of Internal Medicine Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

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